WEST Search History

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DATE: Monday, November 22, 2004

Hide?	Set Name	Query	Hit Count
		DB=PGPB,USPT,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ	
☐	L4	L2 and L3	44
☐	L3	(variant or exercise) induced angina	88
☐	L2	ranolazine	156
☐	L1	6617328.pn.	2

END OF SEARCH HISTORY

h e b b cg b chh e f e ge ge

(FILE 'HOME' ENTERED AT 15:53:17 ON 22 NOV 2004)

FILE 'MEDLINE, HCAPLUS' ENTERED AT 15:53:31 ON 22 NOV 2004

L1	178	S	RANOLAZINE
L2	0	S	PHARMACUETICALLY ACCEPTABLE EXCIPIENT
L3	134	S	PHARMACEUTICALLY ACCEPTABLE EXCIPIENT
L4	0	S	L1 AND L3
L5	6094	S	EXCIPIENT
L6	0	S	L1 AND L5
L7	52091	S	ANGINA
L8	81	S	L1 AND L7

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* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  SEP 01   INPADOC: New family current-awareness alert (SDI) available
 NEWS  4  SEP 01   New pricing for the Save Answers for SciFinder Wizard within
                   STN Express with Discover!
 NEWS  5  SEP 01   New display format, HITSTR, available in WPIDS/WPINDEX/WPIX
 NEWS  6  SEP 27   STANDARDS will no longer be available on STN
 NEWS  7  SEP 27   SWETSCAN will no longer be available on STN
 NEWS  8  OCT 28   KOREAPAT now available on STN
 NEWS  9  NOV 18   Current-awareness alerts, saved answer sets, and current
                   search transcripts to be affected by CERAB, COMPUAB, ELCOM,
                   and SOLIDSTATE reloads

 NEWS EXPRESS  OCTOBER 29 CURRENT WINDOWS VERSION IS V7.01A, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 11 AUGUST 2004
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
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 NEWS WWW      CAS World Wide Web Site (general information)

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FILE 'HOME' ENTERED AT 15:53:17 ON 22 NOV 2004

=> file medline hcaplus
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                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

FILE 'MEDLINE' ENTERED AT 15:53:31 ON 22 NOV 2004

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=> s ranolazine
L1          178 RANOLAZINE

=> s pharmacuetically acceptable excipient
L2            0 PHARMACUETICALLY ACCEPTABLE EXCIPIENT

=> s pharmaceutically acceptable excipient
L3          134 PHARMACEUTICALLY ACCEPTABLE EXCIPIENT

=> s L1 and L3
L4            0 L1 AND L3

=> s excipient
L5         6094 EXCIPIENT
```

=> s L1 and L5
L6 0 L1 AND L5

=> d l1 1-5 ibib abs

L1 ANSWER 1 OF 178 MEDLINE on STN
ACCESSION NUMBER: 2004524328 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15489836
TITLE: Effects of **ranolazine** with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina. Results of CARISA.
AUTHOR: Anonymous
SOURCE: Kardiologiia, (2004) 44 (3) 78.
Journal code: 0376351. ISSN: 0022-9040.
PUB. COUNTRY: Russia: Russian Federation
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20041022
Last Updated on STN: 20041023

L1 ANSWER 2 OF 178 MEDLINE on STN
ACCESSION NUMBER: 2004507474 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15477962
TITLE: Modulation of energy metabolism as an approach to treating heart failure.
AUTHOR: Lopaschuk G D
CORPORATE SOURCE: University of Alberta, Edmonton, Canada.
SOURCE: Cardiovascular journal of South Africa : official journal for Southern Africa Cardiac Society [and] South African Society of Cardiac Practitioners, (2004 Jul) 15 (4 Suppl 1) S2.
Journal code: 100964061. ISSN: 1015-9657.
PUB. COUNTRY: South Africa
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20041013
Last Updated on STN: 20041013
AB Dramatic alterations in energy metabolism can occur in the failing heart. These include a decrease in mitochondrial respiratory chain activity, a decrease in mitochondrial oxidative capacity, and a compensatory increase in glycolysis. While glycolysis increases in the failing heart, glucose oxidation rates are much lower, due to a decrease in mitochondrial oxidative metabolism. The imbalance between glycolysis and glucose oxidation can result in excessive lactate and proton production in the failing hearth, which can decrease cardiac efficiency. At present, no routine therapies are aimed at optimizing energy metabolism in patients with heart failure. However, both experimental studies and small acute trails in heart failure patients have shown that agents that inhibit fatty acid oxidation, which results in a stimulation of glucose oxidation, can increase contractile function and cardiac efficiency in the failing heart. This includes the use of fatty acid oxidation inhibitors such as **ranolazine**, trimetazidine and etomoxir, or the glucose oxidation stimulator, dichloroacetate. Whether this approach proves efficacious for the chronic treatment of heart failure patients remains to be determined.

L1 ANSWER 3 OF 178 MEDLINE on STN
ACCESSION NUMBER: 2004507447 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15477932
TITLE: Inhibiting fatty acid oxidation as a novel therapeutic approach to treating ischaemic heart disease.
AUTHOR: Lopaschuk G D

CORPORATE SOURCE: University of Alberta, Edmonton, Canada.
SOURCE: Cardiovascular journal of South Africa : official journal for Southern Africa Cardiac Society [and] South African Society of Cardiac Practitioners, (2004 Jul) 15 (4 Suppl 1) S1.
Journal code: 100964061. ISSN: 1015-9657.
PUB. COUNTRY: South Africa
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20041013
Last Updated on STN: 20041013

AB During ischaemia, an imbalance between oxygen supply and demand compromises energy supply to the heart muscle. Mitochondrial oxidative metabolism decreases, with fatty acid oxidation dominating as the main source of residual oxidative metabolism. This unfortunately occurs at the expense of glucose oxidation, resulting in an increased production of lactate and protons by the heart. The resultant acidosis in the muscle decreases cardiac efficiency at a time when the heart is already starved of energy. A new approach to treating coronary heart disease involves improving cardiac efficiency by inhibiting fatty acid oxidation and stimulating glucose oxidation. This metabolic approach is beneficial both as monotherapy and combination therapy in the treatment of angina pectoris. Trimetazidine and **ranolazine**, are two clinically effective anti-anginal agents that act by inhibiting fatty acid oxidation, thereby stimulating glucose oxidation and increasing cardiac efficiency. Trimetazidine, which is widely used clinically, acts by inhibiting long chain 3-ketoacyl CoA thiolase (3-KAT), a key fatty acid beta-oxidation enzyme. It is the first of a promising new class of metabolic agents that act by optimising energy metabolism in the heart.

L1 ANSWER 4 OF 178 MEDLINE on STN
ACCESSION NUMBER: 2004504350 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15473411
TITLE: Current and future treatment strategies for refractory angina.
AUTHOR: Yang Eric H; Barsness Gregory W; Gersh Bernard J; Chandrasekaran Krishnaswamy; Lerman Amir
CORPORATE SOURCE: Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic College of Medicine, Rochester, Minn 55905, USA.
SOURCE: Mayo Clinic proceedings, (2004 Oct) 79 (10) 1284-92.
Journal code: 0405543. ISSN: 0025-6196.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Abridged Index Medicus Journals; Priority Journals
ENTRY DATE: Entered STN: 20041012
Last Updated on STN: 20041012

AB Patients with refractory angina are not candidates for revascularization and have both class III or IV angina and objective evidence of ischemia despite optimal medical therapy. An estimated 300,000 to 900,000 patients in the United States have refractory angina, and 25,000 to 75,000 new cases are diagnosed each year. This review focuses on treatment strategies for refractory angina and includes the mechanism of action and clinical trial data for each strategy. The pharmacological agents that have been used are **ranolazine**, ivabradine, nicorandil, L-arginine, testosterone, and estrogen; currently, only L-arginine, testosterone, and estrogen are approved by the Food and Drug Administration. Results with the noninvasive treatments of enhanced external counterpulsation and transcutaneous electrical nerve stimulation are provided. Invasive treatment strategies including spinal cord stimulation, transmyocardial revascularization, percutaneous myocardial

revascularization, and gene therapy are also reviewed.

L1 ANSWER 5 OF 178 MEDLINE on STN
ACCESSION NUMBER: 2004467477 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15378133
TITLE: Antiarrhythmic and proarrhythmic properties of QT-prolonging antianginal drugs.
AUTHOR: Singh Bramah N; Wadhani Nitin
CORPORATE SOURCE: Division of Cardiology, Veterans Administration Greater Los Angeles Healthcare System and the David Geffen School of Medicine at the University of California at Los Angeles, Los Angeles, CA 90073, USA.. bsingh@ucla.edu
SOURCE: Journal of cardiovascular pharmacology and therapeutics, (2004 Sep) 9 Suppl 1 S85-97.
Journal code: 9602617. ISSN: 1074-2484.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20040921
Last Updated on STN: 20041029

AB In recent years there has been a major reorientation of drug therapy for cardiac arrhythmias, its changing role, and above all, a radical change in the class of arrhythmia drugs because of their impact on mortality. The decline in the use of sodium-channel blockers has led to an ex panding use of beta-blockers and simple or complex class III agents for controlling cardiac arrhythmias. Success with these agents in the context of their side effects has spurred the development of compounds with simpler ion-channel blocking properties that have less complex adverse reactions. The resulting so-called pure class III agents, such as dofetilide or ibutilide, were found to have antifibrillatory effects in atrial fibrillation and flutter and in ventricular tachyarrhythmias. Such agents are effective and have diversity, but they have come into therapeutics with a price: the sometimes-fatal torsades de pointes. The drug amiodarone, a complex compound that was synthesized as an antianginal agent, has been an exception in this regard. Its therapeutic use is associated with a negligibly low incidence of torsades de pointes, even though the drug produces significant bradycardia and QT lengthening to 500 to 700 msec. Recent electrophysiologic studies suggest that this paradox is likely due to the differential block of ion channels in endocardium, epicardium, midmyocardial (M) cells, and Purkinje fibers in the ventricular myocardium. There is also clinical evidence suggesting that amiodarone reduces the "torsadogenic" effects of pure class III agents. **Ranolazine** was also synthesized for the development of antianginal properties that stem from a partial inhibition of fatty acid oxidation; it too has been found to have electrophysioloigic properties.. These are somewhat similar to those of amiodarone on ion channels in endocardium, epicardium, M cells, and Purkinje fibers in the ventricular myocardium, but the drug does not prolong the QT interval to the same extent as amiodarone does. Thus, the drug produces modest increases in repolarization as judged by its effects on the action potential duration (APD) without the potential for the development of torsades de pointes. By virtue of its suppressant action on early afterdepolarizations and triggered activity in Purkinje fibers and M cells, the drug appears to have a powerful potential for reducing the torsadogenic proclivity of conventional class III antiarrhythmic compounds. The rationale for the therapeutic niche for amiodarone, and especially in the case of **ranolazine**, in the prevention of drug-induced torsades de pointes is discussed.

=> s angina
L7 52091 ANGINA

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=> s L1 and L7
L8          81 L1 AND L7

=> d L8 1-5 ibib abs

L8   ANSWER 1 OF 81     MEDLINE on STN
ACCESSION NUMBER:   2004524328     IN-PROCESS
DOCUMENT NUMBER:    PubMed ID: 15489836
TITLE:              Effects of ranolazine with atenolol, amlodipine,
                    or diltiazem on exercise tolerance and angina
                    frequency in patients with severe chronic angina.
                    Results of CARISA.
AUTHOR:             Anonymous
SOURCE:             Kardiologiia, (2004) 44 (3) 78.
                    Journal code: 0376351. ISSN: 0022-9040.
PUB. COUNTRY:       Russia: Russian Federation
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           Russian
FILE SEGMENT:       IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE:         Entered STN: 20041022
                    Last Updated on STN: 20041023

L8   ANSWER 2 OF 81     MEDLINE on STN
ACCESSION NUMBER:   2004507447     IN-PROCESS
DOCUMENT NUMBER:    PubMed ID: 15477932
TITLE:              Inhibiting fatty acid oxidation as a novel therapeutic
                    approach to treating ischaemic heart disease.
AUTHOR:             Lopaschuk G D
CORPORATE SOURCE:   University of Alberta, Edmonton, Canada.
SOURCE:             Cardiovascular journal of South Africa : official journal
                    for Southern Africa Cardiac Society [and] South African
                    Society of Cardiac Practitioners, (2004 Jul) 15 (4 Suppl 1)
                    S1.
                    Journal code: 100964061. ISSN: 1015-9657.
PUB. COUNTRY:       South Africa
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE:         Entered STN: 20041013
                    Last Updated on STN: 20041013
AB   During ischaemia, an imbalance between oxygen supply and demand
     compromises energy supply to the heart muscle. Mitochondrial oxidative
     metabolism decreases, with fatty acid oxidation dominating as the main
     source of residual oxidative metabolism. This unfortunately occurs at the
     expense of glucose oxidation, resulting in an increased production of
     lactate and protons by the heart. The resultant acidosis in the muscle
     decreases cardiac efficiency at a time when the heart is already starved
     of energy. A new approach to treating coronary heart disease involves
     improving cardiac efficiency by inhibiting fatty acid oxidation and
     stimulating glucose oxidation. This metabolic approach is beneficial both
     as monotherapy and combination therapy in the treatment of angina
     pectoris. Trimetazidine and ranolazine, are two clinically
     effective anti-anginal agents that act by inhibiting fatty acid oxidation,
     thereby stimulating glucose oxidation and increasing cardiac efficiency.
     Trimetazidine, which is widely used clinically, acts by inhibiting long
     chain 3-ketoacyl CoA thiolase (3-KAT), a key fatty acid beta-oxidation
     enzyme. It is the first of a promising new class of metabolic agents that
     act by optimising energy metabolism in the heart.

L8   ANSWER 3 OF 81     MEDLINE on STN
ACCESSION NUMBER:   2004504350     IN-PROCESS
DOCUMENT NUMBER:    PubMed ID: 15473411
TITLE:              Current and future treatment strategies for refractory
                    angina.
```

AUTHOR: Yang Eric H; Barsness Gregory W; Gersh Bernard J; Chandrasekaran Krishnaswamy; Lerman Amir
CORPORATE SOURCE: Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic College of Medicine, Rochester, Minn 55905, USA.
SOURCE: Mayo Clinic proceedings, (2004 Oct) 79 (10) 1284-92. Journal code: 0405543. ISSN: 0025-6196.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Abridged Index Medicus Journals; Priority Journals
ENTRY DATE: Entered STN: 20041012
Last Updated on STN: 20041012

AB Patients with refractory **angina** are not candidates for revascularization and have both class III or IV **angina** and objective evidence of ischemia despite optimal medical therapy. An estimated 300,000 to 900,000 patients in the United States have refractory **angina**, and 25,000 to 75,000 new cases are diagnosed each year. This review focuses on treatment strategies for refractory **angina** and includes the mechanism of action and clinical trial data for each strategy. The pharmacological agents that have been used are **ranolazine**, ivabradine, nicorandil, L-arginine, testosterone, and estrogen; currently, only L-arginine, testosterone, and estrogen are approved by the Food and Drug Administration. Results with the noninvasive treatments of enhanced external counterpulsation and transcutaneous electrical nerve stimulation are provided. Invasive treatment strategies including spinal cord stimulation, transmyocardial revascularization, percutaneous myocardial revascularization, and gene therapy are also reviewed.

L8 ANSWER 4 OF 81 MEDLINE on STN
ACCESSION NUMBER: 2004467475 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15378131
TITLE: Efficacy and safety of a metabolic modulator drug in chronic stable **angina**: review of evidence from clinical trials.
AUTHOR: Chaitman Bernard R
CORPORATE SOURCE: Saint Louis University School of Medicine, St. Louis, MO 63117, USA.. chaitman@slu.edu
SOURCE: Journal of cardiovascular pharmacology and therapeutics, (2004 Sep) 9 Suppl 1 S47-64. Journal code: 9602617. ISSN: 1074-2484.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20040921
Last Updated on STN: 20041029

AB A number of newer antianginal agents, including nicorandil, trimetazidine, and ivabradine, have been synthesized in recent years, but **ranolazine**, a piperazine derivative that partially inhibits fatty acid oxidation and the late INa current in animal models, is of particular interest mechanistically. Earlier clinical trials with immediate-release **ranolazine** led to the current sustained-release version tested in the Monotherapy Assessment of **Ranolazine** In Stable **Angina** (MARISA) (n = 193) and Combination Assessment of **Ranolazine** In Stable **Angina** (CARISA) trials (n = 823) of patients with chronic **angina** and severe limitation of exercise capacity (ie, < 5 metabolic equivalents). MARISA was a placebo-controlled, randomized trial that compared **ranolazine** monotherapy (500 mg, 1000 mg, and 1500 mg, twice daily) to placebo. CARISA was a placebo-controlled trial that randomized patients on background beta-blocker or calcium antagonist therapy to placebo or

ranolazine (750 mg or 1000 mg, twice daily). Both studies showed a significant increase in total exercise duration, time to **angina** onset, and time to 1 mm ST segment depression. The average magnitude of increase in exercise duration over placebo was 29 to 56 seconds at peak and 24 to 46 seconds at trough with the 3 doses tested in MARISA, and 24 to 34 seconds greater than placebo with the 2 doses used in CARISA. The beneficial effect was achieved without clinically important changes in rest or exercise heart rate or blood pressure. Weekly **angina** attack frequency and nitroglycerin usage were significantly reduced in a dose-dependent manner in the 12-week CARISA trial. Reported adverse effects were similar in MARISA and CARISA and consisted of asthenia, nausea, constipation, and dizziness. Syncope, reported in 8 patients at doses of 1000 mg twice daily or more may be related to attenuation of alpha-1 receptor activity. The mean QTc interval increased with dose and was less than 10 msec on **ranolazine** at 1000 mg twice daily. The mortality rates at 1 and 2 years in MARISA and CARISA open-label run-on studies were 2% and less than 5%, acceptable for this high-risk population with limited exercise capacity. In conclusion, clinical trial evidence with **ranolazine** to date is consistent with its proposed mechanism of action and demonstrates an effective antianginal profile that may benefit patients with severe chronic **angina**.

L8 ANSWER 5 OF 81 MEDLINE on STN
ACCESSION NUMBER: 2004467474 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15378130
TITLE: Myocardial energy metabolism during ischemia and the mechanisms of metabolic therapies.
AUTHOR: Stanley William C
CORPORATE SOURCE: Department of Physiology and Biophysics, School of Medicine, Case Western Reserve University, Cleveland, OH 44106, USA.. wcs4@case.edu
SOURCE: Journal of cardiovascular pharmacology and therapeutics, (2004 Sep) 9 Suppl 1 S31-45.
Journal code: 9602617. ISSN: 1074-2484.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20040921
Last Updated on STN: 20041029

AB The primary effect of ischemia is reduced aerobic adenosine triphosphate (ATP) formation in mitochondria. This triggers accelerated glycolysis and reduced cell pH, Ca(2+) accumulation, K(+) efflux, adenosine formation, and the clinical signs of ischemia: chest pain and a shift in the ST segment. Traditional therapies for **angina** are aimed at either decreasing the need for ATP by suppressing heart rate, blood pressure, and cardiac contractility, or at increasing oxygen delivery to the mitochondria, or both. An additional approach to treating **angina** is to suppress myocardial fatty acid oxidation, increase pyruvate oxidation, and reduce anaerobic glycolysis. High fatty acid levels result in oxygen wasting and inhibit the oxidation of pyruvate in the mitochondria. In experimental models, the partial inhibition of myocardial fatty acid oxidation with agents such as oxfenicine, **ranolazine**, and trimetazidine stimulates glucose oxidation and reduces lactate production during ischemia. Clinical studies demonstrate that this approach is as effective as traditional hemodynamic therapies at improving exercise tolerance and reducing the frequency of **angina** . Moreover, because these agents do not suppress heart rate, blood pressure, or contractility, they are effective as add-on therapy to Ca(2+)-channel and beta-adrenergic receptor antagonists.

=> d L8 76-81 ibib abs

L8 ANSWER 76 OF 81 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:502670 HCAPLUS
DOCUMENT NUMBER: 132:18342
TITLE: **Ranolazine**: an antiischemic drug with a novel mechanism of action
AUTHOR(S): Hara, Akiyoshi; Matsumura, Hisao; Maruyama, Kazuyasu; Hashizume, Hiroko; Ushikubi, Fumitaka; Abiko, Yasushi
CORPORATE SOURCE: Department of Pharmacology, Asahikawa Medical College, Asahikawa, 078-8510, Japan
SOURCE: Cardiovascular Drug Reviews (1999), 17(1), 58-74
CODEN: CDREEA; ISSN: 0897-5957
PUBLISHER: Neva Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 65 refs., describing the pharmacol. profile of **ranolazine** and discussing the mechanism of its myocardial anti-ischemic (or antianginal) action.
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 77 OF 81 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:458642 HCAPLUS
DOCUMENT NUMBER: 131:125138
TITLE: A controlled trial with a novel anti-ischemic agent, **ranolazine**, in chronic stable **angina** pectoris that is responsive to conventional antianginal agents
AUTHOR(S): Pepine, Carl J.; Wolff, Andrew A.
CORPORATE SOURCE: Department of Medicine, Division of Cardiovascular Medicine, University of Florida College of Medicine, Gainesville, FL, 32610-0277, USA
SOURCE: American Journal of Cardiology (1999), 84(1), 46-50
CODEN: AJCDAG; ISSN: 0002-9149
PUBLISHER: Excerpta Medica, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The efficacy and safety of a new anti-ischemic agent, **ranolazine**, were assessed in a randomized, double-blind, placebo-controlled crossover study. At least 1 antianginal drug was withdrawn from the drug regimen of 312 patients with chronic stable **angina** while they took placebo. After exercise time had shortened by ≥1.0 min, the patients were assigned to receive either immediate-release **ranolazine** in 3 dosage regimens or placebo during each treatment period. After each week of treatment, exercise tolerance and plasma **ranolazine** concns. at both peak and trough were measured. All exercise parameters were improved with **ranolazine** (all regimens combined) at mean peak plasma concns. ranging 1576-2492 ng/mL compared with placebo. Although similar trends persisted at mean trough plasma concns. (range 275-602 ng/mL), only the time to 1.0-mm ST-segment depression remained significant. In conclusion, immediate-release **ranolazine** is effective and well tolerated. However, this immediate-release, short-acting formulation at this dosage regimen is not adequate for continuous protection. Either larger or more frequent doses or a sustained-release formulation would be required for clin. use.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 78 OF 81 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:225981 HCAPLUS
DOCUMENT NUMBER: 130:232254
TITLE: Antianginal effects of **ranolazine** in various experimental models of **angina**
AUTHOR(S): Wang, Jin-Xia; Maruyama, Kazuyasu; Murakami, Makoto; Endo, Takuro; Komatsu, Hidetada; Akahane, Masuo

CORPORATE SOURCE: Pharmacological Laboratories, Kissei Pharmaceutical Co. Ltd., Nagano, 399, Japan
SOURCE: Arzneimittel-Forschung (1999), 49(3), 193-199
CODEN: ARZNAD; ISSN: 0004-4172
PUBLISHER: Editio Cantor Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of **ranolazine** (CAS 95635-55-5, KEG 1295), a novel antianginal drug, on the ST-segment changes induced by coronary ligation, epinephrine, and vasopressin were examined following oral or intraduodenal administration. In anesthetized dogs, intraduodenal administration of KEG-1295 (10, 30, or 50 mg/kg) or atenolol (10 mg/kg) significantly attenuated the ST-T wave elevation induced by 2-min coronary ligation imposed during elec. heart pacing (200 beats/min). This antianginal effect of KEG-1295 persisted for 3 h without any changes in hemodynamic parameters, while that of atenolol was accompanied by more or less maintained decreases in diastolic blood pressure, heart rate, and the maximum first derivative of left ventricular pressure. In anesthetized rats, oral administration of KEG-1295 (10, 30, or 50 mg/kg) attenuated the ST-T wave elevation induced by epinephrine (0.3 μg/kg i.v.) in a dose-dependent manner, although KEG-1295 (10 or 30 mg/kg p.o.) failed to attenuate the ST-segment depression induced by vasopressin (0.2 IU/kg i.v.). These findings suggest that, taken orally, KEG-1295 may exert potent protective effects against **angina** pectoris, except that caused by vasospasm. Further, KEG-1295 may be categorized as a new type of antianginal agent, without any primary hemodynamic effects.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 79 OF 81 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:240509 HCAPLUS
DOCUMENT NUMBER: 129:24
TITLE: **Ranolazine**: a novel metabolic modulator for the treatment of **angina**
AUTHOR(S): McCormack, James G.; Stanley, William C.; Wolff, Andrew A.
CORPORATE SOURCE: Diabetes Discovery, Novo Nordisk A/S, Bagsvaerd, DK-2880, Den.
SOURCE: General Pharmacology (1998), 30(5), 639-645
CODEN: GEPHDP; ISSN: 0306-3623
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with .apprx.40 refs. 1. **Ranolazine** shifts ATP production away from fatty acid oxidation toward glucose oxidation 2. Because more oxygen is required to phosphorylate a given amount of ATP during fatty acid oxidation than during carbohydrate oxidation, the **ranolazine**-induced shift in substrate selection reduces the cell's demand for oxygen without decreasing its ability to do work. The shift also maintains coupling of glycolysis to glucose oxidation during ischemia, thus reducing tissue acidosis. 3. This unique, non-hemodynamic mechanism offers the potential to treat **angina** without reducing blood pressure, heart rate or myocardial contractility. 4. At least three double-blind, randomized, placebo-controlled clin. trials have yielded data consistent with this hypothesis.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 80 OF 81 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:629700 HCAPLUS
DOCUMENT NUMBER: 127:287936
TITLE: Effects of **ranolazine** on ischemic threshold, coronary sinus blood flow, and myocardial metabolism in coronary artery disease

AUTHOR(S): Bagger, Jens Peder; Botker, Hans Erik; Thomassen, Anne; Toftgaard Nielsen, Torsten
CORPORATE SOURCE: Department of Cardiology, Skejby Section, Aarhus University Hospital, Aarhus, Den.
SOURCE: Cardiovascular Drugs and Therapy (1997), 11(3), 479-484
CODEN: CDTHET; ISSN: 0920-3206
PUBLISHER: Kluwer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cytoprotection or metabolic modulation is a new principle in the treatment of **angina** pectoris. The effect of **ranolazine** (a cytoprotective drug) on ischemic threshold, coronary sinus blood flow, and myocardial metabolism was evaluated by means of two pacing sequences in nine male patients with coronary artery disease (CAD) and in eight male controls. **Ranolazine** was given as an i.v. bolus followed by continuous infusion; the mean total dose was 32.7 mg and 31.7 mg in patients and controls, resp. **Angina** pectoris was relieved in two patients after **ranolazine** but pacing time to pain was unchanged in the remaining patients. Maximal ST depression was lower (p=0.02), but pacing time to maximal and to 1-mm ST depression remained unchanged after the drug. **Ranolazine** had no overall influence on coronary sinus blood flow, cardiac oxygen consumption, blood pressure, and heart rate. Cardiac uptake of free fatty acids (FFA) was reduced (p=0.01), and net uptakes of glucose (p=0.07) and lactate (p=0.06) tended to be lower after **ranolazine** in CAD patients and controls. **Ranolazine** had no direct influence on cardiac exchange of glutamate, alanine, and citrate or on the arterial concentration of any metabolite. In the present study **ranolazine** had minimal clin. effects. A decrease in myocardial FFA utilization, however, allows greater myocardial glucose oxidation, which may increase the energy production in relation to oxygen availability.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 81 OF 81 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:981641 HCAPLUS
DOCUMENT NUMBER: 124:21477
TITLE: The antianginal agent **ranolazine** is a weak inhibitor of the respiratory complex I, but with greater potency in broken or uncoupled than in coupled mitochondria
AUTHOR(S): Wyatt, Katrina M.; Skene, Caroline; Veitch, Keith; Hue, Louis; McCormack, James G.
CORPORATE SOURCE: Dep. Pharmacology, Syntex Res. Cent., Scotland, EH14 4AP, UK
SOURCE: Biochemical Pharmacology (1995), 50(10), 1599-606
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Ranolazine** (RS-43285) has shown antianginal effects in clin. trials and cardiac anti-ischemic activity in several in vivo and in vitro animal models, but without affecting hemodynamics. Its mechanism is thought to mainly involve a switch in substrate utilization from fatty acids to glucose to, thus, improve efficiency of O2 use; however, its precise mol. target(s) are unknown. In studies to investigate its action further, using isolated rat heart mitochondria, **ranolazine** was found to weakly inhibit (pIC50 values > 300 μM) respiration by coupled mitochondria provided with NAD+-linked substrates but not with succinate. With broken mitochondrial membranes or submitochondrial particles, **ranolazine** inhibited NADH but not succinate oxidation and with pIC50 values in the lower range of 3-50 μM. Studies with different electron

acceptors and respiratory inhibitors indicated that it inhibits respiratory Complex I at a site between ferricyanide and mendadione and ubiquinone-1 reduction (i.e. at a similar locus to rotenone). However, unlike rotenone, **ranolazine** was an uncompetitive inhibitor with respect to ubiquinone-1. **Ranolazine** inhibition of Complex I was reversible and occurred also with mitochondria from pig, guinea pig, and human heart, and rat liver. Further studies using rat heart mitochondria in different energization states (i.e. broken, uncoupled, or coupled) showed a 50-100-fold shift to greater potency of **ranolazine** in the broken compared to the coupled; with the uncoupled it was about 2-fold less potent than the broken. These shifts in potency were not found with rotenone or amytal. Studies with radiolabeled **ranolazine** showed that it bound to mitochondrial membranes with greater affinity in the broken compared to the coupled or uncoupled conditions. Rotenone displaced radiolabeled **ranolazine** from its binding site. This property of **ranolazine** may play some in its anti-ischemic activity.